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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

PTOL-90A (Rev. 04/07)

		Application No.	**Applicant(s)**
Office Action Summary		10/664,234	RUAN ET AL.
		Examiner	**Art Unit**	
		Diana B. Johannsen	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
  Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

    4a) Of the above claim(s) *1-24,42 and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-41 and 44-54* is/are rejected.

7)☒ Claim(s) *27,28,35,37,44-47 and 53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All   b)☐ Some * c)☐ None of:

       1.☐ Certified copies of the priority documents have been received.

       2.☐ Certified copies of the priority documents have been received in Application No. _____.

       3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08)
    Paper No(s)/Mail Date *0806*.

4)☐ Interview Summary (PTO-413)
    Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☒ Other: *sequence alignment*.

DETAILED ACTION

1.   This application has been transferred from Ex. T. O'Farrell to Ex. D. Johannsen.

The application remains assigned to Art Unit 1634.

2.   This action is responsive to the Amendment and Response of August 28, 2006,

the corrected specification amendment of May 4, 2007, and the supplemental Response

(regarding provisional obviousness-type double patenting rejections) of September 10,

2007.

3.   Claims 44-46 and 52 have been amended and claims 53-54 have been added.

Claims 1-24.and 42-43 remain withdrawn from consideration (see paragraph 5 below).

Therefore, claims 25-41 and 44-54 are now under consideration. Applicant's

amendments and arguments have been thoroughly reviewed. **Any rejections and/or**

objections not reiterated in this action have been withdrawn. This action is NON-

FINAL.

4.   With regard to the arguments set forth in the Response of August 28, 2006 that

pertain to withdrawn rejections under 35 USC 102 and/or 35 USC 103, it is noted that

those arguments have been considered but have not been addressed herein because

they are moot. The claims are now rejected on the grounds set forth below.

Election/Restrictions

5.   Claims 1-24 and 42-43 remain withdrawn from further consideration pursuant to

37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Election was made **without** traverse in the reply filed on

December 9, 2005. In light of the species election requirement applied to claim 35 (see

the restriction requirement of October 11, 2005), and applicant's election of Mmel (see

the reply of December 9, 2005), restriction enzymes other than Mmel are also

withdrawn from further consideration. Election was made **without** traverse in the reply

filed on December 9, 2005.

Claim Objections

6.   Claims 27-28 are objected to because of the following informalities: claim 27

recites "creating concatemer of ditags" when it should recite, e.g., "creating a

concatemer of ditags." Appropriate correction is required.

7.   Claims 44-47 and 53 are objected to because of the following informalities: claim

44 recites "nucleotide acid molecule" when it should recite, e.g., "nucleic acid molecule."

Appropriate correction is required.

8.   Claim 35 is objected to because of the following informalities: the claim recites

"the asymmetric recognition site are" when it should recite, e.g., "the asymmetric

recognition sites are." Appropriate correction is required.

9.   Claim 37 is objected to because of the following informalities: the claim recites

"site which is Mmel recognition site" when it should recite, e.g., "site which is a Mmel

recognition site." Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

10.   With regard to the prior rejection of claims 25-41 and 44-52 as being indefinite

over the phrases "3' terminus" and "5' terminus," it is noted that applicants' arguments of

August 28, 2006 are persuasive and that this rejection is therefore withdrawn. The

examiner concurs that the specification at, e.g., page 13 makes clear that these terms

are not limited to a single, terminal nucleotide, but rather refer to a terminal region or

portion.

11.   The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly
> claiming the subject matter which the applicant regards as his invention.

12.   Claims 25-41 and 44-54 are rejected under 35 U.S.C. 112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention.

Claim 25 is indefinite because it is not clear whether the claim is drawn to a

method for "preparing at least one oligonucleotide including at least one ditag," as set

forth in the claim preamble, or to a method of simply creating "at least one ditag," as set

forth in the final "linking" step of the claim. None of the method steps of the claim refer

to an oligonucleotide, and it is not clear whether the claimed method actually requires

preparation of an oligonucleotide, or simply of any "ditag," or whether the "at least one

ditag" of the linking step is considered to constitute an oligonucleotide, etc. Therefore,

clarification is required with regard to how the method steps of the claim actually result

in preparation of an oligonucleotide.

Claim 25 is also indefinite over the recitation of the limitation "the nucleic acid

molecule or fragment thereof" in the "isolating" step because it is not clear how this

recitation limits the claim. The first step of claim 25 requires "producing at least one

nucleic acid molecule," but does not refer to any particular nucleic acid molecule or any

fragment thereof that could constitute "the nucleic acid molecule or fragment thereof" of

the "isolating" step. It is not clear whether the "isolating" step requires isolating the 5'

and 3' terminus of the "at least one nucleic acid molecule" of the "producing step," or whether this isolating may be performed with regard to any single nucleic acid molecule, or any fragment thereof. Further, it appears that the "isolating" step of the claim could encompass simply isolating any fragment of "the nucleic acid molecule" (i.e., such that there is no requirement to isolate the 5' and 3' terminus); however, to the extent that the claim is drawn to such an embodiment, it is also unclear as to how the "linking" step could or would be performed. Clarification is required with regard to how the steps of the claimed method relate to one another.

Claims 26-38 and 44-54 are indefinite because it is not clear whether the claims require preparation of "at least one oligonucleotide comprising at least one ditag" (as set forth in the preamble of claim 26) or of at least one oligonucleotide including at least one ditag flanked by two adapters," as set forth in the final method step. It is noted that the "isolating" step of claim 26 merely requires isolation of the 5' and 3' termini of "the nucleic acid molecule," while the "providing" step of the claim recites providing "at least one nucleic acid molecule flanked by two adaptors." The "isolating" step does not clearly reference the "at least one nucleic acid molecule" of the "providing" step and does not clearly require isolating both 5' and 3' termini of that molecule and the separately referenced "two adapters." Thus, it is not clear what type of oligonucleotide(s) must actually be formed to meet the requirements of the claims.

Claims 29 and 44-54 are indefinite over the recitation "the oligonucleotide comprising" in claim 29. It is noted that claim 26, from which claim 26 depends, refers to "at least one oligonucleotide" but not to a single, specific oligonucleotide. It is not

clear whether the further limitations of claim 29 pertain to the "at least one oligonucleotide" of claim 26 (such that each oligonucleotide encompassed by the method must be included "in a vector"), or whether a method comprising including only a single oligonucleotide of the type referenced in claim 26 in a vector would be embraced by the claims. Clarification is required.

Claim 32 is indefinite over the recitation of the limitation "whereby matching 5' and 3' termini sequences are identified." It is not clear what is encompassed by this limitation. For example, does "matching 5' and 3' termini sequences" refer to 5' and 3' termini sequences that match each other, does this refer to a matching of sequences determined during the practice of the claimed method with database sequences, etc.? Clarification is required.

Claims 33-36 are indefinite over the recitation of the limitation "splicing the 5' terminus and the 3' terminus of the molecule to produce at least one ditag, wherein splicing includes adding at least one restriction enzyme capable of recognizing the recognition sites." First, the claims previously refer to multiple molecules, and it is not clear which of these might constitute "the molecule" of this limitation. Second, as the claims do not previously refer to "recognition sites," it is not clear what is referenced by the term "the recognition sites." Finally, with regard to the recitation "adding at least one restriction enzyme," it is not clear what is meant by this language; to what is the enzyme added? Clarification is required.

Claims 34-36 are indefinite over the recitation of the limitation 'the two

recognition sites" because the claims do not previously refer to or recite "two recognition

sites." It is therefore not clear how claim 34 further limits claims 26 and 33.

Claim 35 is indefinite over the recitation of the limitation "the type II restriction

enzyme is...." Because the claim previously refers to "type II restriction enzymes" but

not to a single particular enzyme. Thus, it is not clear whether this limitation further

limits the previously recited "type II restriction enzymes" or whether this language limits

only one of the multiple enzymes encompassed by the claim.

Claim 37 is indefinite because it is not clear how the claim further limits claim 26,

from which it depends. Specifically, it is not clear whether the claim recites further

limitations on the steps previously recited in claim 26, or whether the claim recites steps

that are to be performed in addition to those set forth in claim 26. To the extent that the

claim may be drawn to the latter, it is also unclear as to how the additional steps relate

to the objective of "preparing at least one oligonucleotide," etc.

Claim 37 is also indefinite over the recitation of the phrase "producing at least

one full-length cDNA molecule comprising two adapters flanking the 5' terminus and 3'

terminus" because it is not clear whether this language requires two adapters at each

end of the molecule, or one adaptor at each end of the molecule. Clarification is

required.

Claim 39 is indefinite over the recitation of the method step "defining the

structural region of the corresponding gene on the genome map." It is noted that the

neither the specification nor the prior art provide a clear definition for this terminology,

and it is not clear whether this language requires any kind of manipulation or action on the part of a practitioner, or whether the "defining" of the claim inherently results from the previously recited method step. Clarification is required with respect to how "defining the structural region..." actually relates to or affects the actually manipulative steps of the claimed method.

Claims 40-41 are indefinite over the recitation of the limitation "the obtained at least one ditag" in claim 40 because the claim never refers to, e.g., obtaining a ditag (rather, the claim refers to preparation of an oligonucleotide containing a ditag). This rejection could be overcome by amending the claim to delete the word "obtained."

Claims 40-41 are also indefinite because the "comparing" step of claim 40 requires comparing with a map "and/or" a database, while the subsequent "detecting" step requires detecting both with respect to the genome map AND one or more database. To the extent that the claims are drawn to methods in which the comparing step encompasses only comparing with a map OR a database, it is unclear how the final step of the method (and therefore the method as a whole) could be performed.

Claim 41 is indefinite over the recitation of the limitation "recovering the full-length nucleic acid molecule corresponding to the newly discovered gene." First, as the claims do not previously refer to a "newly discovered gene," it is not clear what entity or molecule is referenced by the limitation "the newly discovered gene." Second, it is not clear what is meant by the term "recovering." For example, does this term refer to or require any type of physical step or manipulation, or would it encompass simply

reading a database entry corresponding to a "full-length" gene (such that there is no

manipulative difference between claims 40-41)? Clarification is required.

Claims 44-47 and 53 are indefinite over the recitation of the phrase "the vector

comprises an isolated oligonucleotide" in claim 44 because it is not clear how the

referenced oligonucleotide could be considered "isolated" if it is present in the recited

vector. It is suggested that the term "isolated" be deleted from the claim.

Claim Rejections - 35 USC § 102

13.   The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that

form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14.   Claims 25-31, 33-35, 37-38, 44-49, and 53 are rejected under 35 U.S.C. 102(b)

as being anticipated by Macevicz (US 6,136,537 [issued 24 October 2000]).

It is first noted that the specification does not provide a limiting definition for the

term "ditag." At page 4, the specification refers to "two tags (a ditag) per nucleic acid

molecule," such that this language broadly encompasses any two "tag" sequences that

may be obtained from a single nucleic acid molecule.

Macevicz discloses a modification of the serial analysis of gene expression

(SAGE) method in which pairs of sequence tags are constructed using a portion of each

end of a target polynucleotide such as a cDNA (see entire reference, particularly the

summary at col 2, line 17-col 3, line 19). Macevicz discloses, e.g., a method in which a

nucleic acid molecule of interest is inserted into a vector, and subsequently cleaved,

linearized, and recircularized to form a tag pair or "ditag" including the 5' and 3' terminus

of the nucleic acid molecule (see, e.g., col 2, lines 32-67). Macevicz further discloses

producing the nucleic acid molecules employed in their methods (see, e.g., col 4, lines

20-65; col 8, line 21-col 9, line 3); Macevicz therefore discloses all 3 steps of claim 25,

and anticipates that claim.

Regarding claim 26 and claims dependent therefrom, Macevicz also discloses

the production and use in his method of nucleic acid molecules flanked by linkers so as

to produce ditags flanked by linkers (see, e.g., col 4, lines 20-65, particularly lines 50-

52; col 6, lines 26-52); it is a property of such linkers that they constitute a type of

adaptor. Macevicz also explicitly discloses the ligation of adaptors to the ends of

nucleic acid molecules at, e.g., col 10, lines 19-45. Accordingly, Macevicz anticipates

claim 26. Regarding claims 27-28, Macevicz discloses a step of creating concatemers

of ditags (see, e.g., col 2, lines 64-67; col 9, lines 46-55). Regarding claim 28, Macevicz

teaches concatemers of several hundred base pairs, and therefore discloses quantities

of ditags meeting the requirements of claim 28 in a single concatemer molecule.

Regarding claim 30, Macevicz discloses RNA including mRNA, as well as various

cDNAs (both truncated and full length) (see, e.g., col 8, lines 21-col 9, line 3), and also

discloses the use of genomic DNA (see, e.g., col 2, lines 32-35). With respect to claim

31, Macevicz discloses sequencing of ditags to determine gene expression (see, e.g.,

col 9,lines 52-55). Regarding claims 33-35 and 37, it is again noted that Macevicz

discloses the addition of linkers/adaptors (see, e.g., col 4, lines 20-65, particularly lines

50-52; col 6, lines 26-52; col 10, lines 19-45), and that Macevicz further discloses the

use of multiple adaptors comprising multiple asymmetric recognition sites, and specifically discloses the elected Mmel restriction site (see, e.g., col 10, lines 10-45; col 7, lines 28-50, particularly line 52; see also col 4, line 37). With further regard to claim 37, Macevicz specifically disclose the use of such adaptors with cDNA at, e.g., col 10, lines 41-45. Regarding claim 38, Macevicz discloses ditags comprising 34-38 nucleotides; see, e.g., col 9, line 64.

Regarding claim 29 and claims dependent therefrom, it is again noted that Macevicz teaches construction of his ditags in a vector (see again col 2, lines 17-67; see also col 6, line 26-col 7, line 27). Regarding claims 44-49 and 53, vectors and adaptors meeting the requirements of the claims are disclosed at, e.g., col 10, lines 10-45, and the disclosure of Mmel is again noted (see col 4, line 37 and col 7, line 52). With further regard to claims 46-49, it is also noted that Macevicz teaches selection of a vector "which does not contain a recognition site...for the type IIs enzyme(s) used to generate pairs of segments; otherwise, re-circularization cannot be carried out" (see col 7, lines 43-47).

15.   Claims 25 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Macevicz (US 6,054,276 A [25 April 2000]; hereinafter referred to as Macevicz-II).

It is again noted that the specification does not provide a limiting definition for the term "ditag." At page 4, the specification refers to "two tags (a ditag) per nucleic acid molecule," such that this language broadly encompasses any two "tag" sequences that may be obtained from a single nucleic acid molecule.

Macevicz-II discloses methods of genomic mapping and gene expression monitoring in which pairs of sequences obtained from each end of a restriction fragment are employed (see entire reference, particularly the summary at col 1, line 60-col 2, line 56). In preferred embodiments, Macevicz-II discloses providing populations of restriction fragments or cDNAs, excising each end thereof, ligating the ends together to form pairs, and employing the pairs or concatenations thereof in mapping, sequence analysis, etc. (see, e.g., col 2, lines 15-56; col 3, line 65-col 4, line 10; claims 5-6). These steps of providing nucleic acids, excising the 5' and 3' ends thereof and ligating them together result in the formation of a molecule that constitutes an oligonucleotide including at least one "ditag" as set forth in applicants' specification, and thus Macevicz-II anticipates claim 25. Regarding claim 39, Macevicz-II also discloses the use of concatemers of multiple ditags obtained from nucleic acid populations including cDNAs (such that the molecules "correspond to" the "full-length of a gene or fragment thereof"), and disclose employing such concatemers in mapping, which results in "defining the structural region of the corresponding gene on the genome map," as required by the claims (see, e.g., col 2, lines 40-56; col 7, line 64-col 8, line 61). Thus, Macevicz-II anticipates claim 39.

Claim Rejections - 35 USC § 103

16.   The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17.   This application currently names joint inventors. In considering patentability of

the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g)

prior art under 35 U.S.C. 103(a).

18.   Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over

Macevicz (US 6,136,537 [issued 24 October 2000]) in view of Saha et al (Nature

Biotechnology 19:50—512 [5/2002]).

        Macevicz discloses a modification of the serial analysis of gene expression

(SAGE) method in which pairs of sequence tags are constructed using a portion of each

end of a target polynucleotide such as a cDNA (see entire reference, particularly the

summary at col 2, line 17-col 3, line 19). Macevicz discloses, e.g., a method in which a

nucleic acid molecule of interest is inserted into a vector, and subsequently cleaved,

linearized, and recircularized to form a tag pair or "ditag" including the 5' and 3' terminus

of the nucleic acid molecule (see, e.g., col 2, lines 32-67). Macevicz further discloses

producing the nucleic acid molecules employed in their methods (see, e.g., col 4, lines

20-65; col 8, line 21-col 9, line 3). Macevicz also discloses the production and use in

his method of nucleic acid molecules flanked by linkers so as to produce ditags flanked

by linkers (see, e.g., col 4, lines 20-65, particularly lines 50-52; col 6, lines 26-52); it is a property of such linkers that they constitute a type of adaptor. Macevicz also explicitly discloses the ligation of adaptors to the ends of nucleic acid molecules at, e.g., col 10, lines 19-45.

While Macevicz discloses the sequencing of ditags to determine gene expression (see, e.g., col 9, lines 52-55), Macevicz does not disclose comparing ditag sequences to a database comprising genomic sequences and identification of "matching" 5' and 3' termini.

Like Macevicz, Saha et al disclose methods in which short sequence tags obtained from gene transcripts are employed in expression analysis (see entire reference). Saha et al disclose querying the human genome sequence database to determine the genes corresponding to tags (see page 509). As the tags of Macevicz comprise the 5' and 3' termini of the nucleic acid molecules being analyzed, the performance of the method of Saha et al using the tags of Macevicz would result in matching both 5' and 3' termini, as required by the claim.

In view of the teachings of Saha et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Macevicz so as to have performed the further step taught by Saha et al of querying genetic databases to identify genes corresponding to the ditags of Macevicz. Saha et al teach that such further analysis of expression tags is "complementary to other approaches for gene identification," allows "identification of regions not annotated by other methods," and is "an order of magnitude more efficient" than EST sequencing

(see page 510, right column). Thus, an ordinary artisan would have been motivated to

have made such a modification in order to have achieved any of these advantages

specifically taught by Saha et al.

19.   Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over

Macevicz (US 6,136,537 [issued 24 October 2000]) in view of Belfort et al (Nucleic

Acids Research 25(17):3379-3388 [1997]).

Macevicz discloses a modification of the serial analysis of gene expression

(SAGE) method in which pairs of sequence tags are constructed using a portion of each

end of a target polynucleotide such as a cDNA (see entire reference, particularly the

summary at col 2, line 17-col 3, line 19). Macevicz discloses, e.g., a method in which a

nucleic acid molecule of interest is inserted into a vector, and subsequently cleaved,

linearized, and recircularized to form a tag pair or "ditag" including the 5' and 3' terminus

of the nucleic acid molecule (see, e.g., col 2, lines 32-67). Macevicz further discloses

producing the nucleic acid molecules employed in their methods (see, e.g., col 4, lines

20-65; col 8, line 21-col 9, line 3). Macevicz also discloses the production and use in

his method of nucleic acid molecules flanked by linkers so as to produce ditags flanked

by linkers (see, e.g., col 4, lines 20-65, particularly lines 50-52; col 6, lines 26-52); it is a

property of such linkers that they constitute a type of adaptor. Macevicz also explicitly

discloses the ligation of adaptors comprising asymmetric restriction sites to the ends of

nucleic acid molecules at, e.g., col 10, lines 19-45. However, Macevicz does not

disclose the use of asymmetric restriction sites that "are homing endonuclease

asymmetric recognition site sequences" recognized by any of the enzymes set forth in

claim 36.

Belfort et al teach that homing endonucleases are rare-cutting enzymes (see

entire reference, particularly page 3379 and 3385, right column), and that such

enzymes include I-Ceul, PI-Scel, PI-Pspl, and I-Scel (see, e.g., Table 2). In view of the

teachings of Belfort et al, it would have been *prima facie* obvious to one of ordinary skill

in the art at the time the invention was made to have modified the method of Macevicz

so as to have employed adaptors including restriction sites for any of the

endonucleases taught by Belfort et al, including any of I-Ceul, PI-Scel, PI-Pspl, and I-

Scel. It is noted that Macevicz teaches selection of a vector for use in his methods

"which does not contain a recognition site...for the type IIs enzyme(s) used to generate

pairs of segments; otherwise, re-circularization cannot be carried out" (see col 7, lines

43-47). Thus, it would have been obvious to an ordinary artisan to have selected for

use in adaptors any recognition site for a rare-cutting enzyme (including any of those

taught by Belfort et al) for the advantage of employing recognition sites that would be

less likely to be present in a vector used in the method of Macevicz.

20.   Claims 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Macevicz (US 6,054,276 A [25 April 2000]; hereinafter referred to as Macevicz-II) in

view of Saha et al (Nature Biotechnology 19:50—512 [5/2002]).

Macevicz-II discloses methods of genomic mapping and gene expression

monitoring in which pairs of sequences obtained from each end of a restriction fragment

are employed (see entire reference, particularly the summary at col 1, line 60-col 2, line

56). In preferred embodiments, Macevicz-II discloses providing populations of restriction fragments or cDNAs, excising each end thereof, ligating the ends together to form pairs, and employing the pairs or concatenations thereof in mapping, sequence analysis, etc. (see, e.g., col 2, lines 15-56; col 3, line 65-col 4, line 10; claims 5-6). The ligating of ends and concatemerization of pairs taught by Macevicz-II results in the formation of molecules that constitute oligonucleotides including at least one "ditag" as set forth in applicants' specification, and including "joined" tags as set forth in the claims. Macevicz-II also discloses the use of concatemers of multiple ditags obtained from nucleic acid populations including cDNAs in mapping (see, e.g., col 2, lines 40-56; col 7, line 64-col 8, line 61), and particularly teaches comparing ditags with a map at, e.g., col 8, lines 20-50. However, Macevicz-II does not teach "detecting no match on one or more gene database," as set forth in claim 40, or the further step set forth in claim 41 of "recovering the full-length nucleic acid molecule" corresponding to a newly discovered gene.

Like Macevicz-II, Saha et al disclose methods in which short sequence tags obtained from gene transcripts are employed in expression analysis and genome mapping (see entire reference). Saha et al disclose querying the human genome sequence database to determine the genes corresponding to tags (see page 509), and disclose the further analysis of unmatched tags that "represent potential undiscovered genes or unrecognized exons of previously annotated genes" by PCR of DLD-1 cell cDNA followed by further analysis (see page 510). The unmatched tags taught by Saha et al have "no match on one or more gene database," as set forth in claim 40, and the

PCR taught by Saha et al constitutes "recovering" a "full-length nucleic acid molecule" corresponding to a newly discovered gene, as required by claim 41. In view of the teachings of Saha et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Macevicz-II so as to have performed the further steps taught by Saha et al of querying genetic databases to identify both previously identified and novel genes corresponding to the ditags of Macevicz-II, and to have further analyzed and characterized any unmatched ditags using the steps suggested by Saha et al. Saha et al teach that such further analysis of expression tags is "complementary to other approaches for gene identification," allows "identification of regions not annotated" by other methods," and is "an order of magnitude more efficient" than EST sequencing (see page 510, right column). Thus, an ordinary artisan would have been motivated to have made such a modification in order to have achieved any of these advantages specifically taught by Saha et al.

Comment regarding third party submission

21. A third-party submission has been filed under 37 CFR 1.99 on May 11, 2005 in the published application.

To ensure that a third-party submission does not amount to a protest or pre-grant opposition, 37 CFR 1.99 does not permit the third party to have the right to insist that the examiner consider any of the patents or publications submitted. Furthermore, if the submission or part of the submission is not in compliance with 37 CFR 1.99, that noncompliant submission or part thereof will not be entered in the application file.

Therefore, unless the examiner clearly cites a patent or publication on form PTO-892, Notice of References Cited and such reference is used in a rejection or its relevance is actually discussed during prosecution, consideration by the examiner of any patent or publication submitted in a third-party submission cannot be presumed.

If the applicant wants to ensure that the information in a third-party submission is considered by the examiner, the applicant should submit the information in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98. An individual who has a duty to disclose under 37 CFR 1.56 should also submit any material information contained in a third-party submission to the Office in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98 to ensure such material information is properly disclosed to the examiner.

In the instant case, it is noted that applicants have already cited the references provided in the third-party submission in an IDS (filed August 28, 2006), and that the three references cited in the third party submission have been considered by the examiner. Velculescu et al is drawn to an improvement of SAGE methods employing long ditags; it is also noted that Velculescu et al disclose the use of Mmel as a tagging enzyme (see entire reference, particularly paragraph 20). Both Macevicz references have been considered and applied in prior art rejections as set forth above.

Double Patenting

22. The obviousness-type double patenting rejection over claims 1-3 and 5 of co-pending application 11/145,005 set forth in the Office action of February 27, 2006 is **withdrawn**. It is noted that claims 1-3 and 5 of the '005 application have been

canceled, and that the claims of the instant application are patentably distinct from the

claims now pending in the '005 application.

23.   The nonstatutory double patenting rejection is based on a judicially created
doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the
unjustified or improper timewise extension of the "right to exclude" granted by a patent
and to prevent possible harassment by multiple assignees. A nonstatutory
obviousness-type double patenting rejection is appropriate where the conflicting claims
are not identical, but at least one examined application claim is not patentably distinct
from the reference claim(s) because the examined application claim is either anticipated
by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140
F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29
USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.
1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422
F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163
USPQ 644 (CCPA 1969).
        A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d)
may be used to overcome an actual or provisional rejection based on a nonstatutory
double patenting ground provided the conflicting application or patent either is shown to
be commonly owned with this application, or claims an invention made as a result of
activities undertaken within the scope of a joint research agreement.
        Effective January 1, 1994, a registered attorney or agent of record may sign a
terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with
37 CFR 3.73(b).

24.   Claim 25 is provisionally rejected on the ground of nonstatutory obviousness-type

double patenting as being unpatentable over claims 1-19 and 24-25 of copending

Application No. 11/045,468 (corresponding to published application US 2005/0255501

A1). Although the conflicting claims are not identical, they are not patentably distinct

from each other because claim 25 is anticipated by the '468 claims. Specifically,

independent claim 1 of the '468 application includes steps of preparing a nucleic acid

molecule fragment (which constitutes "producing" a nucleic acid molecule as set forth in

instant claim 25), and isolating and linking the 5' and 3' termini of the fragment to create

at least one ditag (see step (ii) of claim 1 of the '468 application). Although the '468

claims do not, e.g., include a recitation of "preparing" an oligonucleotide including a

ditag, these steps of claim 1 inherently result in the preparation of such an

oligonucleotide; thus, the '468 claims anticipate instant claim 25.   This is a provisional

obviousness-type double patenting rejection because the conflicting claims have not in

fact been patented.

25.   With regard to the obviousness-type double patenting rejection over copending

application 11/045,468 set forth in the Office action of February 27, 2006, it is noted that

applicant requested in the Response of September 10, 2007 that the rejection be held in

abeyance until claims of the instant application have found to be in condition for

allowance. Applicant's request is noted. Claim 25 is now rejected for the reasons set

forth above.

Conclusion

26.   It is noted that the prior art does not teach or suggest methods employing a

vector comprising SEQ ID NO: 18 (see claim 50 and claims dependent therefrom),

which vector was derived by applicants from the prior art pGEM3z vector as described

in the specification at, e.g., pages 33-34, and customized for use in their methods. As

illustrated in the alignment provided herewith, instant SEQ ID NO: 18 is 79.3% identical

to pGEM3z (which constitutes the closest prior art reference with respect to the vector

of SEQ ID NO: 18).

27.   Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Diana B. Johannsen whose telephone number is
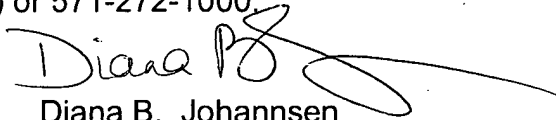
571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634

```
RESULT 2
CVPGEM3Z
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2004
DEFINITION    Cloning vector pGEM-3Z.
ACCESSION     X65304
VERSION       X65304.3  GI:7018282
KEYWORDS      beta-lactamase; bla gene; cloning vector; lacZ gene; multiple
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SOURCE        Cloning vector pGEM-3Z
  ORGANISM    Cloning vector pGEM-3Z
              other sequences; artificial sequences; vectors.
REFERENCE     1
  AUTHORS     Technical,Services.
  TITLE       Direct Submission
  JOURNAL     Submitted (23-MAR-1992) Technical Services, Promega Corporation,
              2800 Woods Hollow Road, Madison, Wi 53711-5399, USA
  REMARK      revised by [2]
REFERENCE     2
  AUTHORS     Technical,Services.
  TITLE       Direct Submission
  JOURNAL     Submitted (28-MAY-1993) Technical Services, Promega Corporation,
              2800 Woods Hollow Road, Madison, Wi 53711-5399, USA
  REMARK      revised by [3]
REFERENCE     3
  AUTHORS     Technical,Services.
  TITLE       Direct Submission
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              2800 Woods Hollow Road, Madison, Wi 53711-5399, USA
  REMARK      revised by [4]
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  TITLE       Direct Submission
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COMMENT       On Feb 21, 2000 this sequence version replaced gi:6782312.
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WI.
              Call one of the following numbers for order or technical
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              Order or Technical 800-356-9526
              In Wisconsin        800-356-9526
              Outside U.S.        608-274-4330.
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Qy      3033 CCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGG
3092
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2372 CCCGGAGACGGTCACAGCTTGTCTGTAAGCGGATGCCGGGAGCAGACAAGCCCGTCAGGG
2431

Qy      3093 CGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTAACTATGCGGCATCAGAGCAGAT
3152
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db      2432  CGCGTCAGCGGGTGTTGGCGGGTGTCGGGGCTGGCTTAACTATGCGGCATCAGAGCAGAT
2491

Qy      3153  TGTACTGAGAGTGCACCATATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATA
3212
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2492  TGTACTGAGAGTGCACCATATGCGGTGTGAAATACCGCACAGATGCGTAAGGAGAAAATA
2551

Qy      3213  CCGCATCAGGCGCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCG
3272
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2552  CCGCATCAGGCGCCATTCGCCATTCAGGCTGCGCAACTGTTGGGAAGGGCGATCGGTGCG
2611

Qy      3273  GGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTG
3332
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      2612  GGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGATGTGCTGCAAGGCGATTAAGTTG
2671

Qy      3333  GGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATA
3392
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||·||||||
Db      2672  GGTAACGCCAGGGTTTTCCCAGTCACGACGTTGTAAAACGACGGCCAGTGAATTGTAATA
2731

Qy      3393  CGACTCACTATA 3404
              ||||||||||||
Db      2732  CGACTCACTATA 2743
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